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EXAMINER	
LEAVITT, MARIA GOMEZ	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,098	GOLETZ ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,11,12 and 23-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,11,12 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05-25-2010 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3, 5, 6, 11, 12 and 23-30 are currently pending. Claims 1, 3 and 11 have been amended and claims 25-30 have been added by Applicants' amendment filed on 05-25-2010.

Therefore, claims 1, 3, 5, 6, 11, 12 and 23-30 are currently under examination to which the following grounds of rejection are applicable

Withdrawn Objections/Rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 102

In view of the Examiner's interpretation of the phrase "wherein the TF is exposed" recited in claims 1, 3 subpart (c), and 11, as a cell line wherein TF present on GPA and MUC1 has been exposed due to incomplete endogenous *O*-glycosylation of mucins or sialidase treatment of the cell line so as to generate MUC1 molecules with exposed TF, and AGPA molecules with exposed TF, as detected by binding of specific antibodies, rejection of claim 1 under 35 U.S.C. §102(b) as being anticipated by Ichiyama M (2000, Kari Igaku Kenkyusho Zasshi, JP vol. 51, no. 3-4, pages 93-110, of record) as evidenced by Benoist et al., (1992,

Immunology Letters, pp. 45-55) and Karsten et al., (1998, Cancer Research pp. 2541-2549, of record) has been withdrawn.

Ichiyama M does not describe a cell line which expresses TF, MUC1 and glycophorin wherein TF is exposed as reflected by binding of specific antibodies.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections/objections maintained in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 103

Claims 1, 5, 6, 11, 12, 23 and **24** remain rejected and new **claims 26 and 28** are rejected under 35 USC 103 as being unpatentable over Ichiyama M (2000, Kari Igaku Kenkyusho Zasshi, JP vol. 51, no. 3-4, pages 93-110, of record) as evidenced by Hinoda (2005, Journal of Clinical Laboratory Analysis, pages 100 – 104, Abstract), in view of Benoist et al., (Immunology Letters 1992, pp. 45-55) and Karsten et al., (1998, Cancer Research pp. 2541-2549, of record), and further in view of Horton et al., (U.S. Patent 7,268,120, Date of filing Apr. 21 2000) and Springer G (1997, J Mol Med, pp. 594-602, of record).

Ichiyama M, discloses the cell line K562 contransfected with tumor-associated epithelial human mucin MUC1cDNA and with human B7cDNA (Figures 1-12) **(Current claim 1, in part; claim 5, claim 6, in part)**. Note that B7 is a cell surface costimulatory molecule mediating interactions between T cells and APC and K562 is a human erythroleukemic cell line (page 2)**(Current claims 26 and 28)**. In addition, Ichiyama M, established a co-culture protocol using the cancer vaccine cell line MUCI/B7 contransfected K562 and a mixed lymphocyte tumor cell culture (MLTC) to stimulate, for example, growth of PBMC (p. 99, Fig. 4) **(Current claims 11 and 12, in part).** Ichiyama describes that the MUC1 molecule are present on normal epithelial

cells and a peptide epitope with strong immunogenicity is covered by rich sugar chains and is exposed when glycosylation fails due to canceration (page 6) . In addition, Ichiyama discloses detection of MUC1 with the monoclonal antibody (MAb) MUSE11 which recognizes the continuous amino acid sequence PDTRPAPG as evidenced by Hinoda. The examiner believes this is the same sequence recognized by the TA-specific antibody and identified in the specification as filed at page 7, lies 5-10, as tumor-associated MUC1 epitope, i.e. TA-MUC1. The TA-MUC1 is commonly known in the art and dffers from normal MUC1 by modified glycan side chains, absent evidence to the contrary **(Current claim 24)**.

Ichiyama M, do not specifically teach expression of glycophorin in K562.

However, at the time the invention was made, Benoist teaches that the K562 tumor cells present glycophorin A (GPA) on the cell surface. Indeed, Benoist discloses that increase of GPA expression on the cell surface may correlate with the resistance of K562 to NK cells (Abstract) (Current claim 1, in part).

The combined disclosure of Ichiyama M. and Benoist fails to teach the presence of TF in the cell line K562.

However, at the time the invention was made, Karsten discloses the presence of the TF antigen (Galβ1-3GalNAcα-O-Ser/Thr (Core 1)) and Tn antigen (GalNAcα-O-Ser/Thr) at different single and multiple positions within the immunodominat region of the MUC1 repeat (p. 2541, col. 2, paragraphs 1-2) **(Current claim 1, in part)**. Moreover, Karsten discloses that reduced glycosylation of MUC1, due to deletion of glycosyltransferases, permits the immune system access to the peptide core of the mucin. Further, nonglycosylated immunodominat DTR motif in MUC1 has been detected in breast cancer patients (p. 2541; col. 1). Further, Karsten

teaches that alloreactive cytotoxic T-cell clones from patients with colorectal carcinoma were shown to kill preferentially MUC1-expressing target cells by recognizing underglycosilated VNTR peptide in conjunction with an internal carbohydrate epitope, the TF-disaccharide (p. 2549; col. 1) clearly underscoring the immunogenicity of the TF in nonglycosylated DTR motif in MUC1.

The combined disclosure of Ichiyama M, Benoist and Karsten fails to teach that enzymatic removal of the sialic acid covering the T antigen disaccharide in glycophorin to obtain asialoglycophorin to enhance the immune effect of GPA.

However, at the time the invention was made, Springer teaches that crude preparations of enzymatically desialylated glycophorin from O RBC carrying high densities of TF in a pharmaceutical vaccine elicited specific TF-specific DTR responses reflecting activation of specific T cell (**Current claims 1 and 23**).

The combined disclosure of Ichiyama M, Benoist and Karsten fails to teach transformation of the cell line K562 with a vector encoding at least a cytokine, MHC I, and others) as required by claim 6.

However, at the time the invention was made, Horton is an exemplified prior art that teaches that it is routine or well-established in the art to employ *ex vivo* polynucleotide constructs and selective transfection of malignant cells containing polynucleotides expressing therapeutic or prophylactic molecules (col. 1, lines 20-25) . Moreover, Horton discloses polynucleotide constructs encoding an interferon and an additional cytokine or an immunomodulatory molecule, i.e., MHC class I antigen, tumor antigen, and co-stimulatory molecule (col. 32, lines 35-45).

Horton describes examples of well known tumor-associated antigenic and immunogenic antigens, including TF and MUC1 (col. 47, lines 65-67) **(Current claim 6, in part).**

Therefore, in view of the benefits of a cancer vaccine cell line K562 that expresses MUC1/B7 after transfection with a vector encoding said molecules to induce anti-tumor effector cells as taught by Ichiyama M, said cell line K562 further comprising on the cell surface TF and glycophorin as disclosed by Benoist and Karsten, it would have been *prima facie* obvious for one of ordinary skill in the art, to provide TF or MUC1 and glycophorin as tumor antigens with unmasked TF (e.g., exposed TF) in the cell line K562 by digestion of sialic acids with neuramidase treatment to unmask TF to effectively stimulate T-cell proliferation in an attempt to improve the efficacy of the vaccine formulation, as a person of ordinary skill in the art has good reason to pursue options within his grasp. Moreover, it would have been *prima facie* obvious for one of ordinary skill in the art, as a matter of design of choice, to modify the K562 cell line by transfection with a nucleic acid encoding an epitope to enhance the immunogenic response (e.g., cellular and humoral) against said cancer epitopes, particularly because transfection of malignant cells containing polynucleotides expressing therapeutic or prophylactic molecules was well known in the art as taught by Horton. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. One of ordinary skill in the art would have had a reasonable expectation of success in generating a cell line which expresses on the surface TF, MUC1 and glycophorin and any additional nucleic acid encoding one or more polypeptides as evidenced by the production of tumor cell lines in the instant specification by following the combined teachings of Ichiyama M, Benoist, Karsten, Horton and Springer.

The response to Applicants' Arguments filed on 05-25-2010 as it applies to rejection of claims 1, 5, 6, 11, 12, 23, 24, 26 and 28 under ***35 USC 103***

At page 5 of the remarks filed on 05-25-2010, Applicants essentially argue that the claims 1, 3 and 11 have been amended to facilitate prosecution to recite the phrase "wherein the TF is exposed" as suggested by the Examiner in the Office action of October 28, 2009. Such is not persuasive.

Applicants have not submitted new arguments to rebut rejection of claims 1, 5, 6, 11, 12, 23, 24, 26 and 28 under 35 USC § 103 which was previously maintained in the Office Actions filed on 01-14-2010 and 02-25-2010. Of note, Figure 1 in the specification evidences that wild type K562 cells before magnetic separation express TF, Tn, GPA, AGPA and MUC1 markers. What applicants have obtained with enzymatic desialylation with neuramidase treatment is an enriched population K562-derived cell for TF, i.e., NM-F9 and NM-D4. Therefore, claims 1, 5, 6, 11, 12, 23, 24 , 26 and 28 remain rejected under 35 USC 103 for the reasons already of record and the reasons set forth in the paragraph above.

New grounds of rejection

Objection Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see ¶s [0023], [0039] of the published application, for example. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3, 5, 6, 11, 12 and 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3 subpart (c) , and 11 are indefinite in the recitation of the phrase "wherein the TF is exposed". The O-glycan Core 1 (Galβ1-3GalNAcα-O-), also called Thomsen-Friedenreich disaccharide (TF), is a cryptic structure that is present at different single and multiple positions within the immunodominat region of the mucin 1 (MUC1) repeat and in glycophorin A (GPA). Note that asialoglycophorin (AGPA) consists of the carrier protein glycophorin and TF groups in high amounts. Indeed, the specification as filed discloses that GPA of NM-F9 is almost free of sialic acids and most of the 15 TF groups exposed resembling asialoglycophorin A (AGPA) (¶ [0131] of the published application). Therefore, it is unclear whether the TF is exposed on the surface of the claimed cell line because of recombinant expression of TF, or genetically modification to exposed cryptic structures in MUC1 and GPA comprising TF, or that GPA exists as asialoglycophorin (AGPA) on the membrane of the cell line. Moreover, it is unclear what the TF is exposed to, e.g. antibodies, blood, serum, ligand, glycosyltransferases and others. Therefore, the metes and bounds of "wherein the TF is exposed" are indefinite.

Claims 5, 6, 12 and 23-30 are indefinite insofar as they depend from claim 1.

For the purpose of a compacted prosecution claims 1, 3, 5, 6, 11, 12 and 23-30 have been interpreted as a cell line wherein TF present on GPA and MUC1 has been exposed due to incomplete endogenous *O*-glycosylation of mucins or sialidase treatment so as to generate a cell

line comprising TF-positive GPA, and TF-positive MUC1 as detected by binding of specific antibodies.

Claim Rejections - 35 USC § 112- First paragraph- New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claim 25 recites "wherein the cell line is obtained from a TF-negative cell line". Claim 26 recites "wherein the cell line is obtainable from an immortalized cell line" . The response dated 05/25/2010 indicates that support for the above new limitations regarding a TF-negative cell line and an immortalized cell line could be found at paragraphs 12, 14 and 15 of the published application. However, a review of paragraphs 12, 14 and 15 and the specification as filed reveals no specific disclosure of "wherein the cell line is obtained from a TF-negative cell line". What the specification does disclose regarding a TF-negative cell line is that the claimed cell line recited in claim 1 can "be generated from any cell line which expresses endogenously or recombinantly MUC1 and glycophorin, preferably K562 cells", that the cells are analyzed for TF

expression and in case, the number of TF-positive cells is to low, the TF-negative cell line is treated with a mutagen, preferably a chemical mutagen, preferably ethyl methanesulfonate (EMS)(see¶s [0012] [0016]of the published application). There is nothing more to lead one of skill in the art to appreciate that TF-negative cell lines was a part of the invention, as opposed to cell lines that endogenously or recombinantly express MUC1 and glycophorin with low number of TF-positive cells as detected by flow cytometry or immunocytochemistry. Furthermore, a review of paragraphs 12, 14 and 15, and the specification as filed reveals no specific disclosure of "wherein the cell line is obtainable from an immortalized cell line". A review of the specification as filed reveals no specific disclosure of generation of the cell line of claim 1 from any immortalized cell line. What the specification does disclose regarding the term "cell line" is that "cells of a single type that have been grown in the laboratory for several generations" ¶ [0016]of the published application. Classically, an established or immortalized cell line has acquired the ability to proliferate indefinitely either through random mutation or deliberate modification whereas most primary cell cultures have limited lifespan (e.g. a few passages in culture). There is nothing more to lead one of skill in the art to appreciate cell lines obtained from an immortalized cell line other than K562-a human erythroleukemic cell line.

Therefore, there appears to be no support for the limitations of "wherein the cell line is obtained from a TF-negative cell line" or for " wherein the cell line is obtainable from an immortalized cell line" Thus, the amended claims include impermissible New Matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 28 and 29 are rejected under rejected under 35 USC 103 as being unpatentable over Ichiyama M (2000, Kari Igaku Kenkyusho Zasshi, JP vol. 51, no. 3-4, pages 93-110, of record) as evidenced by Hinoda (2005, Journal of Clinical Laboratory Analysis, pages 100 – 104, Abstract), in view of Benoist et al., (Immunology Letters 1992, pp. 45-55) and Karsten et al., (1998, Cancer Research pp. 2541-2549, of record), and further in view of Horton et al., (U.S. Patent 7,268,120, Date of filing Apr. 21 2000) and Springer G (1997, J Mol Med, pp.

594-602, of record) as applied to claims **1, 5, 6, 11, 12, 23, 24 , 26 and 28** above and further in view of Suzuki (Mutat Res 1997 pp.75-82)

The combined disclosure of Ichiyama M, Benoist, Karsten, Horton and Springer are outlined in the paragraphs above.

The combined disclosure of Ichiyama M, Benoist, Karsten, Horton and Springer fails to teach a cell line generated by chemical mutagenesis with ethyl methanesulfonate (EMS).

However, at the time the invention was made, Suzuki exemplifies prior art wherein mutagenic agents such as ethyl methane sulfonate (EMS) are used for induction of gene mutations and chromosomal aberrations at the O6 position of guanine (Abstract).

Therefore, in view of the benefits of a cancer vaccine cell line K562 that expresses MUC1/B7 after transfection with a vector encoding said molecules to induce anti-tumor effector cells as taught by Ichiyama M, said cell line K562 further comprising on the cell surface TF and glycophorin as disclosed by Benoist and Karsten, it would have been *prima facie* obvious for one of ordinary skill in the art, as a matter of design of choice, to generate a cell line that synthesizes and expresses on the cell surface TF, MUC1 and glycophorin after treatment with a mutagenic agent, such as ethyl methane sulfonate as taught by Suzuki, as a person of ordinary skill in the art has good reason to pursue options within his grasp. The generation of transgenic cell lines by exposure to mutagenic agents is within the ordinary level of skill in the art of molecular biology.

Thus, all of the elements of the claims were known to one of ordinary skill in the art at the time the invention was made and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions and the combination

would have yielded nothing more than predictable results to one of ordinary skill in the art at the time of invention.

Thus, in view of the foregoing, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

Claims 1, 3, 5, 6, 11, 12 and 23-30 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
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